REMARKS

This application has been carefully reviewed in light of the Office Action dated August 5, 2009. Applicant respectfully requests consideration of the foregoing amendment in light of the following remarks.

Summary of the Office Action

In the Office Action of August 5, 2009, claims 1-3, 5, 7, 8, 11, 12, 15, 30, 31, 33, 35, 36, 39, 40, 42 and 44-47 were rejected under 35 U.S.C. 103(a) as allegedly being obvious over the article to Okamato et al. in Nature Biotechnol., vol. 18, pp. 438-441 (hereinafter referred to as "Okamato"), in view of U.S. Patent No. 6,839,454 to Park (hereinafter referred to as "Park"), WO 99/39817 to Rava et al. (hereinafter referred to as "Rava"), U.S. Patent No. 5,624,711 to Sundberg et al. (hereinafter referred to as "Sundberg"), U.S. Patent No. 6,569,979 to Strother et al. (hereinafter referred to as "Strother"), U.S. Patent No. 6,127,129 to Corn et al. (hereinafter referred to as "Corn"), and U.S. Patent No. 7,191,901 to Maxim et al. (hereinafter referred to as "Maxim"). No other issues were raised.

Status of the Application

Upon entry of the present amendment, claims 1-2, 12 and 15 will have been amended, and claims 30-56 will have been canceled. Accordingly, claims 1-29 remain pending in the application, with claims 4, 6, 9-10, 13-14 and 16-29 having been withdrawn as drawn to a non-elected invention.

Rejection of Claims 1-3, 5, 7, 8, 11, 12, 15, 30, 31, 33, 35, 36, 39, 40, 42 and 44-47 under 35 U.S.C. 103(a) over Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim

Claims 1-3, 5, 7, 8, 11, 12, 15, 30, 31, 33, 35, 36, 39, 40, 42 and 44-47 were rejected under 35 U.S.C. 103(a) as allegedly being obvious over Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim (*see, e.g.,* pages 2-9 of Office Action). This rejection is respectfully traversed.

Claims 30-31, 33, 35, 36, 39, 40, 42 and 44-47 are being canceled with the present amendment, and thus the rejection of these claims is rendered moot.

Claim 1 is not obvious over the teachings of Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim, because none of the references teaches or suggests a method for producing a probe carrier comprising:

"(1) *a step of preparing 100 or more kinds of purified probes*;

(2) a step of obtaining probe information on each purified probe;

(3) a step of judging "good" or "not good" quality of each purified probe according to the obtained probe information and a predetermined criterion;

(4) a step of obtaining a probe of which quality is "good" in case of the purified probe of which quality is judged as "not good";

(5) a step of individually dissolving each purified probe judged as "good" in a solvent for ejection to a carrier, based on at least a part of the probe information obtained in (2), at a predetermined concentration and storing each obtained probe solution in an individual storing container;

(6) *a step of transferring each probe solution stored in said storing container to another container for containing the probe solutions, respectively, equipped in an apparatus for deposition onto the carrier, the apparatus comprising 100 or more ink jet nozzles and the containers for containing the probe solutions, corresponding to the number of ink jet nozzles*;

(7) a step of applying a surface treatment to the carrier for fixing the probe;

(8) a step of depositing said probe solution onto a treated surface of said carrier by a method including the following steps, thereby forming a plurality of mutually independent probe fixation areas;

(8-1) a step of executing an analytical inspection on the carrier subjected to said surface treatment and judging "good" or "not good" state of said carrier according to the result of said analytical inspection and a predetermined criterion, wherein the predetermined criterion comprises a measurement of a contact angle;

(8-2) *a step of depositing said plural probe solutions onto the carrier* judged as "good" *by using the apparatus for deposition such that probe deposition areas independent for each probe solution are arranged as spots of liquid droplets*;

(8-3) a step of executing an inspection, concerning a formed state of the probe deposition area, on the carrier on which said probe deposition area is formed, and judging "good" or "not good" state of said deposition according the result of said inspection and a predetermined criterion;

(8-4) a step of executing, on the carrier having the probe deposition area judged as "good", a fixation of the probe to the surface of the carrier thereby obtaining a probe carrier;

(8-5) a step of executing an analytical inspection on the probe in at least one of the plural probe fixation areas constituted of probes fixed on said carrier; and

(8-6) a step of judging "good" or "not good" state of the produced probe carrier according to the result of said analytical inspection and a predetermined criterion" (emphasis added), as recited in the claim.

Embodiments of the method as claimed may thus include the steps of *preparing 100 or more kinds of purified probes*, and then *depositing plural probe solutions*, each containing an individual one of the 100 or more probes, by *using*

an apparatus comprising 100 or more ink jet nozzles and containers for containing the probe solutions, with each container corresponding to one of the ink jet nozzles and receiving one the plural probe solutions (*see, e.g.,* paragraphs [0156]-[0158] of publication of instant application). The deposition further proceeds *such that probe deposition areas independent for each probe solution are arranged as spots of liquid droplets*. Aspects of the method may thus provide for the *simultaneous* deposition of the 100 or more different kinds of plural probes onto the carrier, thereby providing for improved control in the production of a probe array with improved quality (*see, e.g.,* paragraphs [0156]-[0158]).

To clarify further, Applicant has discovered that control of the environment at the time of deposition of the probes can be a factor in the production of probe arrays having improved quality. In particular, Applicant has found that such probe arrays can be produced by selecting for carrier surfaces having a "good" state, via measurement of contact angle (*see, e.g.,* paragraphs [0137]-[0138]), as well as *by controlling the deposition of the plural probes onto the carrier surface*, for example via technology that allows for the application of 100 or more minute liquid droplets to a surface, such as ink-jet technology, so as to provide substantially simultaneous deposition thereof (*see, e.g.,* paragraphs [0156]-[0158]).

Applicant noted that a problem with the deposition of small (i.e. minute) liquid droplets onto a carrier is that the droplets tend to start drying almost from the moment they are deposited as spots on the carrier. That is, immediately after the minute liquid droplets are brought into contact with the carrier surface, the solvent used for the droplets starts evaporating, and the components of the liquid droplet may additionally also start reacting with substances on the carrier surface. Thus, for droplets having a small volume, a noticeable change in state can occur over time. Such problems may be exacerbated in conventional droplet deposition methods, which are unable to deposit all of the intended probe solutions onto the carrier in one operation. As a result, the probe solutions are

required to be periodically exchanged for new solutions, with the spotting operation being repeated a plurality of times. Consequently, the spots that have been deposited to the carrier surface before exchanging the probe solution are subject to any subsequently occurring processes (e.g., drying out and/or reacting with substances on the carrier surface), over a period of time that is longer than that of the spots deposited after exchanging the probe solution. Such conventional methods may thus be likely to yield levels of probe binding that substantially vary from one spot to another.

Accordingly, Applicant has discovered a method for obtaining a probe array with more uniform levels of probe binding, by using ink-jet technology to perform steps including *preparing 100 or more kinds of purified probes* and then *using an apparatus comprising 100 or more ink jet nozzles to individually deposit each of the probes*. By providing the ink-jet technology that is capable of simultaneously depositing the 100 or more probe solutions on the carrier, in the form of independent spots of liquid droplets, the variability induced by differences in elapsed time from deposition of the spots can be reduced, thereby increasing the uniformity of the environment experienced by the drops, and reducing the likelihood of variability in levels of probe binding among the spots resulting from differences in the deposition environment.

The method as claimed is not obvious over the teachings of Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim, because none of the references teaches or suggests a method of *preparing 100 or more kinds of purified probes* and then *using an apparatus comprising 100 or more ink jet nozzles to individually deposit each of the probes* in independent deposition areas on a carrier that are arranged as spots of liquid droplets, as recited in the claim. With regard to Okamoto, it is noted that the reference teaches the use of a bubble-jet method for microarray fabrication (*see, e.g.,* Abstract), and discloses examples of such microarray fabrication (*see, e.g.,* page 439). In one example disclosed therein, Okamoto discloses that "[w]e first fabricated eight-by-eight spot

microarrays that contained *the same 18-mer oligonucleotide probe* in each spot to examine the efficacy of our method" (emphasis added, page 439, first full paragraph in left hand column), by placing "the DNA solution *into one of the 200 µl tubes connected to a Bubble Jet printing head BC-62*, which is equipped for ejecting six ink samples from the BJC-700J printer" (page 439, first full paragraph of left hand column). Thus, in this example, Okamoto teaches preparing only *one*, not 100 or more different types of oligonucleotides, and thus does not teach or suggest the step of preparing the probes as claimed. Okamoto further teaches using a printing head that is equipped to eject *only six* samples, and thus does not teach or suggest performing a step of depositing the probes as claimed with an apparatus having *100 or more ink jet nozzles*. Accordingly, the method for producing the probe carrier as claimed is not obvious over this example of Okamoto.

Okamoto teaches a further example wherein microarray comprising 64 oligonucleotide probes is prepared (*see, e.g.,* page 439). According to this example, the deposition of the oligonucleotides was achieved by using "two aligned BC-62 heads to simultaneously eject six DNA solutions, *replacing the DNA solutions after each ejection*. This enabled us to eject 12 different DNA solutions" (emphasis added, page 439, first full paragraph of right hand column). Thus, Okamoto teaches preparing *64 oligonucleotide probes*, but does not teach or suggest preparing *100 or more kinds of probe*, as recited in the claim. Okamoto further teaches using an apparatus that is capable of simultaneously *ejecting 12 different DNA (oligonucleotide) solutions*, but does not teach or suggest deposition solutions using an apparatus *having 100 or more ink jet nozzles*, as recited in the claim. Instead, Okamoto relies on replacing the DNA solutions after each ejection until all 64 oligonucleotide samples have been ejected. Accordingly, as Okamoto does not teach or suggest the preparation and deposition steps as claimed, it is considered that the method as recited is patentable over the teachings of Okamoto.

It is furthermore noted that Okamoto even *teaches against* the method as claimed by teaching that, in the deposition of the 64 oligonucleotides using the two BC-62 printing heads, "[w]e observed a slight disorder of the ejected spots, due to the head structure and the alignment error" (page 439, first full paragraph of right hand column). Okamoto thus indicates that the use of the printing heads for the simultaneous ejection of multiple solutions could have the disadvantage of producing deposited spots that are disordered.

Also, it is noted that Okamoto teaches that "[a]nother problem is the drying of droplets once they have been deposited on substrates" (page 438, first full paragraph of right hand column), to address which Okamoto teaches that "[w]e therefore optimized the DNA ejection solvent to improve volatility, solubility, wettability, viscosity and surface tension of [the] DNA solution, and to promote spot separation" (page 438, second full paragraph of right hand column). Okamoto thus teaches that problems with the drying of droplets can be remedied by optimizing the DNA ejection solvent. Accordingly, it is considered that one of ordinary skill in the art would not have found it obvious to devise the method as claimed, where an apparatus having 100 or more ink jet nozzles is used for the deposition of 100 or more kinds of probes, because Okamoto teaches that any problem with the drying of the droplets can be solved by optimizing the solvent, and further discloses that the simultaneous ejection of multiple solutions can even have disadvantageous results, in terms of the production of disordered spots. Thus, the method of claim 1 is considered to be patentable over the teachings of Okamoto.

Park does not make up for the deficiencies of Okamoto. Instead, Park teaches a method for quantitatively processing a plurality of nucleic acid species expressed in a microarray (*see, e.g.,* Abstract). In particular, Park teaches a method where a computer can be used to process a digital image of the microarray to identify a sub-grid therein (*see, e.g.,* Abstract). Park does not teach or suggest *preparing 100 or more kinds of purified probes* and then *using*

an apparatus comprising 100 or more ink jet nozzles to individually deposit each of the probes in independent deposition areas on a carrier that are arranged as spots of liquid droplets, as recited in the claim. Accordingly, it is considered that the method of claim 1 is patentable over the combined teachings of Okamoto and Park.

Rava does not make up for the deficiencies of Okamoto and Park. Rava teaches a method for quality control in a manufacturing process, in which the arrays may be manufactured by methods including ink jet synthesis (*see, e.g.,* Abstract). However, Rava does not teach or suggest *preparing 100 or more kinds of purified probes* and then *using an apparatus comprising 100 or more ink jet nozzles to individually deposit each of the probes* in independent deposition areas on a carrier that are arranged as spots of liquid droplets, as recited in the claim. Accordingly, it is considered that the method of claim 1 is patentable over the combined teachings of Okamoto, Park and Rava.

Sundberg also does not make up for the deficiencies of Okamoto, Park and Rava. Instead, in the section referred to in the Office Action, Sundberg teaches an example wherein the degree of specific and non-specific binding of strepavidin with slide surfaces was determined via fluorescence microscopy. However, Sundberg does not teach or suggest *preparing 100 or more kinds of purified probes* and then *using an apparatus comprising 100 or more ink jet nozzles to individually deposit each of the probes* in independent deposition areas on a carrier that are arranged as spots of liquid droplets, as recited in the claim. Accordingly, it is considered that the method of claim 1 is patentable over the combined teachings of Okamoto, Park, Rava and Sundberg.

Strother does not make up for the deficiencies of Okamoto, Park, Rava and Sundberg. Strother is referred to in the Office Action for its teachings regarding the measurement of contact angles to determine the extent of deprotection of a surface (*see, e.g.,* column 8, lines 46-64). However, Strother

also does not teach or suggest *preparing 100 or more kinds of purified probes* and then *using an apparatus comprising 100 or more ink jet nozzles to individually deposit each of the probes* in independent deposition areas on a carrier that are arranged as spots of liquid droplets, as recited in the claim. Accordingly, it is considered that the method of claim 1 is patentable over the combined teachings of Okamoto, Park, Rava, Sundberg and Strother.

Corn also does not make up for the deficiencies of Okamoto, Park, Rava, Sundberg and Strother. Corn provides examples in which PM-FT-IRRAS measurements and contact angle measurements are used to evaluate a substrate (*see, e.g.,* column 11, line 52 through column 12, line 6). However, Corn does not teach or suggest *preparing 100 or more kinds of purified probes* and then *using an apparatus comprising 100 or more ink jet nozzles to individually deposit each of the probes* in independent deposition areas on a carrier that are arranged as spots of liquid droplets, as recited in the claim. Accordingly, it is considered that the method of claim 1 is patentable over the combined teachings of Okamoto, Park, Rava, Sundberg, Strother and Corn.

Finally, Maxim does not make up for the deficiencies of Okamoto, Park, Rava, Sundberg, Strother and Corn. Maxim teaches evaluating slides to determine water contact angles and background fluorescence (*see, e.g.,* column 5, lines 10-31). However, Maxim does not teach or suggest *preparing 100 or more kinds of purified probes* and then *using an apparatus comprising 100 or more ink jet nozzles to individually deposit each of the probes* in independent deposition areas on a carrier that are arranged as spots of liquid droplets, as recited in the claim. Accordingly, it is considered that the method of claim 1 is patentable over the combined teachings of Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim.

Claims 3, 5, 7-8 and 11-12 depend from claim 1, and thus are also patentable over Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim, for at least the same reasons as their base claim.

Claim 2 is patentable over the teachings of Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim, because none of the references teaches or suggests a method for producing a probe carrier comprising:

"(a) *a step of designing 100 or more kinds of probes for detecting a target substance*;

(b) a step of synthesizing each of the designed probes;

(c) a step of individually purifying each of the synthesized probes;

(d) a step of obtaining probe information on each purified probe;

(e) a step of judging "good" or "not good" state of synthesis and purification in each purified probe according to the obtained probe information and a predetermined criterion;

(f) a step of repeating the foregoing steps (b) to (e) on the purified probe of which state of synthesis and purification is judged as "not good", thereby obtaining "good" state of synthesis and purification in all the purified probes;

(g) a step of individually dissolving each purified probe judged as "good" in a solvent for ejection to a carrier, based on at least a part of the probe information obtained in (d), in a predetermined concentration and storing each obtained probe solution in an individual storing container;

(h) *a step of transferring each probe solution in the storing container to another container for containing the probe solutions, respectively, equipped in an apparatus for deposition onto the carrier, the apparatus comprising 100 or more ink jet nozzles and the containers for containing the probe solutions, corresponding to the number of the ink jet nozzles*;

(i) a step of applying a surface treatment for fixing the probe to the carrier;

(j) a step of depositing the probe solution onto a treated surface of the carrier by a method including following steps, thereby forming a plurality of mutually independent probe fixation areas;

(j-1) a step of executing an analytical inspection on the carrier for judging "good" or "not good" state of the carrier according to the result of the analytical inspection and a predetermined criterion, wherein the predetermined criterion comprises a measurement of a contact angle;

(j-2) *a step of depositing the plural probe solutions onto the carrier judged as "good" by using the apparatus for deposition such that probe deposition areas independent for each probe solution are arranged as spots of liquid droplets*;

(j-3) a step of executing an inspection, concerning a formed state of the probe deposition area, on the carrier on which the probe deposition area is formed, and judging "good" or "not good" state of the deposition according the result of the inspection and a predetermined criterion;

(j-4) a step of executing, on the carrier having the probe deposition area judges as "good", a fixation of the probe to the surface of the carrier thereby obtaining a probe carrier;

(j-5) a step of executing an analytical inspection on the probe in at least one of the plural probe fixation areas constituted of probes fixed on the carrier; and

(j-6) a step of judging "good" or "not good" state of the produced probe carrier according to the result of the analytical inspection and a predetermined criterion" (emphasis added), as recited in the claim.

As similarly discussed for claim 1 above, neither the Okamoto, Park, Rava, Sundberg, Strother, Corn nor the Maxim reference teaches or suggests *designing 100 or more kinds of probes* and then *using an apparatus comprising 100 or more ink jet nozzles to individually deposit each of the probes* in independent deposition areas on a carrier that are arranged as spots of liquid droplets, as recited in the claim. Accordingly it is considered that the method of

claim 2 is patentable over the teachings of Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim.

Claim 15 is patentable over the teachings of Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim, because none of the references teaches or suggests a method for producing a probe carrier having plural probes fixed on a surface of a carrier, the method comprising:

"a step of executing an analytical inspection on a surface of said carrier and judging "good" or "not good" state of said carrier according to the result of said analytical inspection and a predetermined criterion, wherein the predetermined criterion comprises a measurement of a contact angle;

a step of depositing plural probe solutions onto said carrier judged as "good" by using an apparatus for deposition, the apparatus comprising 100 or more ink jet nozzles and containers for containing the probe solutions, corresponding to the number of ink jet nozzles, such that probe deposition areas independent for each probe solution are arranged as spots of liquid droplets;

a step of executing an inspection, concerning a formed state of said probe deposition area, on the carrier on which said probe deposition area is formed, and judging "good" or "not good" state of said deposition according the result of said inspection and a predetermined criterion;

a step of executing, on the carrier having said probe deposition area judged as "good", a fixation of the probe to the surface of the carrier thereby obtaining a probe carrier;

a step of executing an analytical inspection on the probe in at least one of the plural probe fixation areas constituted of probes fixed on said carrier; and

a step of judging "good" or "not good" state of the produced probe carrier according to the result of said analytical inspection and a predetermined criterion" (emphasis added), as recited in the claim.

As similarly discussed for claim 1 above, neither the Okamoto, Park, Rava, Sundberg, Strother, Corn nor the Maxim reference teaches or suggests

using an apparatus comprising 100 or more ink jet nozzles to individually deposit plural probe solutions in independent deposition areas on a carrier that are arranged as spots of liquid droplets, as recited in the claim. Accordingly it is considered that the method of claim 15 is also patentable over the teachings of Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim.

Accordingly, claims 1-3, 5, 7, 8, 11, 12 and 15 are believed to be patentable over the teachings of Okamoto, Park, Rava, Sundberg, Strother, Corn and Maxim, and the rejection of the claims under 35 U.S.C. 103(a) over these references is respectfully requested to be withdrawn.

CONCLUSION

Applicant respectfully submits that all of the claims pending in the application meet the requirements for patentability, and respectfully requests that the Examiner indicate the allowance of such claims. Any amendments to the claims which have been made in this response, and which have not been specifically noted to overcome a rejection based upon prior art, should be considered to have been made for a purpose unrelated to patentability, and no estoppel should be deemed to attach thereto.

If any additional fee is required, please charge Deposit Account Number 502456. Should the Examiner have any questions, the Examiner may contact Applicant's representative at the telephone number below.

Respectfully submitted,

12/4/2009

Date

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